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ORIGINAL ARTICLE

The feasibility and correlation of atrial fibrillation vulnerability test to the indices of atrial substrates using atrial burst decremental pacing

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Abstract Pulmonary vein isolation and atrial substrate modification using catheter ablation have been developed as a standard treatment for atrial fibrillation (AF). However, the standard end-point for these procedures is still not well established. This study aimed to investigate the characteristics among positive and negative AF vulnerability patients with normal structural heart, in order to define the endpoint of the atrial substrate modification. Fifty supraventricular tachycardia patients with normal heart structure referred for electrophysiological study and catheter ablation were enrolled. After eliminating the underling arrhythmias, the basic cycle length, effective refractory period of the right atrium, and the P wave indices in 12-lead electrocardiograms were measured. The AF vulnerability test was performed by atrial burst decremental pacing with a pacing cycle length decreasing from 290 ms to 200 ms. The AF vulnerability test was considered as positive when the duration of the induced AF or atrial tachyarrhythmias (ATs) was longer than 10 seconds. The parameters of atrial substrates were compared between patients with positive and negative values of the AF vulnerability test. ATs or AF were induced in 24 (48%) patients. Among these patients, 12 (24%) induced ATs or AF were found to be sustained (duration more than 10 seconds). However, only two of these patients could reproduce the positive result after 10 minutes of the first induced protocol. Comparing the patient baseline characteristics, P wave characteristics and cardiac echo parameters, there were no significant differences between the positive and negative AF vulnerability groups. In conclusion, AF and ATs could be induced in patients with a structurally normal heart. The traditional clinical indices of atrial substrates were not significantly different between the positive and negative AF vulnerability patients. Protocols other than

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atrial burst decremental pacing should be investigated to evaluate the endpoint of the atrial substrate modification.

Introduction

Initiating triggers and atrial substrates are the two major components contributing to the occurrence and maintenance of atrial fibrillation (AF) [1,2]. Elimination of initiating triggers and maintenance of atrial substrates are two important strategies for management of AF [3,4]. Catheter ablation with pulmonary veins isolation and atrial substrates modification can eliminate the initiating triggers and modify the atrial substrates for maintenance of AF, and have been developed as a treatment strategy for patients with symptomatic, drug-refractory AF [3,4]. However, the end-point of catheter ablation of AF has not been clearly established.

Previous studies have reported that noninducibility of atrial tachyarrhythmias (ATs) after catheter ablation was a good predictor of a low recurrence rate of AF after pulmonary vein isolation [5,6]. However, ATs could also be induced in patients who had atrioventricular nodal re-entry tachycardia (AVNRT) or atrioventricular reciprocating tachycardia (AVRT) with or without history of AF [7]. The mechanisms of the inducibility test and its relationship to the atrial substrates are still not totally understood [7,8]. The purpose of this study was thus to investigate the characteristics of atrial substrates among positive and negative AF vulnerability test patients with normal structural heart, in order to definite the endpoint of the atrial substrate modification.

Materials and methods

Study participants

Fifty patients with paroxysmal supraventricular tachycardias (PSVT) referred for electrophysiological study and catheter ablation were enrolled. All patients had a detailed review of their disease history. The dimensions of the left atrium (LA) and left ventricle (LV), and the ejection fraction (EF) of the LV were measured by transthoracic echocardiography according to the American Society of Echocardiography guidelines [9]. No evidence of AF according to data from Holter electrocardiography recording and from detailed symptoms suggesting AF could be detected in any patient.

Electrophysiological study and catheter ablation

All patients received electrophysiological study and catheter ablation in a postabsorptive, nonsedated state after informed consent was obtained. All antiarrhythmic drugs were discontinued for at least five half-lives before the electrophysiological study. Three multipolar electrode catheters were positioned in the high right atrium, His-bundle area, and right ventricle, via the right femoral vein. One decapolar electrode catheter was introduced from the right internal jugular vein and placed in the coronary sinus to record the electrical activity around the posteroseptal area and coronary sinus. Intracardiac bipolar electrograms and 12-lead electrocardiogram (ECG) were displayed and recorded by a computer recording system (Bard LabSystem PRO EP Recording System version; Bard, Electrophysiology Division, Lowell, MA, USA) for further analysis. A programmed electrical stimulator (DTU-210; Bloom Associates, Reading, PA, USA) was used to deliver electrical impulses of 2.0-ms duration at approximately twice the diastolic threshold. The mechanisms of PSVT were determined by criteria proposed by previous reports [10,11]. Catheter ablation was performed after diagnosis of mechanisms of PSVT. Techniques used for catheter ablation were the same as described in previous reports [10,11].

AF vulnerability test

After the catheter ablation, the AF vulnerability test was performed. Continuously decremental atrial pacing from HRA with a pacing cycle length decreasing from 290 ms to 200 ms was performed on the patient in order to induce AF or ATs. The positive AF vulnerability test was considered significant when the duration of the induced AF or ATs was longer than 10 seconds. In order to prevent the effect of acute atrial electrical remodeling by rapid atrial pacing, the test was measured repeatedly three times after 10 minutes rest to determine the reproducibility of the results.

Measurements of the effective refractory period and P wave indices

The effective refractory period (ERP) of the right atrium, the P wave indices in each lead of the surface ECG and the sinus cycle length for each patient were measured according to previous study definition after catheter ablation [12]. The ERP of the right atrium was measured by introducing the S2 extrastimulus after eight regularly paced S1—S1 at a basic pacing cycle length of 400 ms. The ERP of the right atrium was then defined as the longest S_1—S_2 interval when the S_2 could not be captured by the atrium tissue.

The P wave indices including the P waver duration, P wave amplitude, and P wave duration dispersion (PWD) were measured manually by digital caliper at a sweep speed of 50 mm/second and amplified 32 times on a computer recording system. The onset of the P wave was defined as the point of first upward slope from baseline for positive wave and as the point of first downward slope from baseline for negative waveforms. The P wave offset was defined as the return to baseline. The mean duration of P wave in each lead of ECG was obtained by measuring P wave duration of three consecutive sinus beats. The PWD was defined as the difference between the mean maximum P wave duration and the mean minimum P wave duration in the 12-lead ECG. The amplitude of P wave was measured by peak amplitude of P wave in a monophasic P wave and peak-to-peak amplitude in a biphasic P wave. The mean amplitude of P wave in each lead was obtained by measuring P wave amplitude of three consecutive sinus beats.

Clinical follow-up

All studied patients received regular follow-up at the outpatient clinic. All possible symptoms and signs suggesting the attack of tachyarrhythmia were surveyed and recorded. The 12-lead surface ECGs were examined and reviewed in the follow-up visits.

Statistical analysis

All data are expressed as mean ± S.D. Continuous variables in the two groups were compared using an independent *t* test. Noncontinuous variables in the two groups were compared using the Chi-square test. A p value of <0.05 was considered significant. All statistical operations were performed using SPSS software (version 11.0, SPSS Inc, Chicago, IL, USA).

Results

Fifty patients (24 males) with PSVT were enrolled in this study. The mean age of the patients was 46 ± 14 years. Among these patients, only seven had hypertension and none had diabetes mellitus or other systemic diseases. The mean value of the patients' LA, LV end diastolic dimension and the LVEF were calculated as 33 ± 6 mm, 45 ± 5 mm and 69 ± 10% respectively.

Thirty-three patients were diagnosed AVNRT and 17 AVRT after the complete cardiac electrophysiology study. All patients then received successful catheter ablation with no recurrence noted in follow-up visits.

From the electrophysiological studies, the mean of the basic sinus cycle length, the right atrium ERP, the maximal mean P wave duration and the mean PWD were calculated as 767 ± 135 ms, 234 ± 23 ms, 124 ± 12 ms, and 34 ± 13 ms, respectively. The mean maximal amplitude of P wave was 0.13 ± 0.04 mV.

After catheter ablation, continuously decremental pacing from pacing cycle length from 290 to 200 ms was performed. A nonsustained AF or ATs was induced in 24 (48%) patients in which 17 patients were AVNRT and seven patients were AVRT. The duration of the induced ATs varied from 936 ms to 185,481 ms. However, only 12 (24%) patients whose induced AF or ATs lasted more than 10 seconds were considered as positive AF vulnerability. After 10 minutes of rest, the identical stimulation protocol was performed again to evaluate the reproducibility of the results. Interestingly, after 3 repeated tests, the sustained ATs or AF could only be reinduced in two out of 12 of the previous positive patients.

In Table 1, the characteristics of the positive and negative AF vulnerability test patients are compared and demonstrated. The distributions of sex and hypertension were not significantly different between patients with and without significant inducibility of ATs. There were also no significant differences in basic sinus cycle length (746 ± 156 vs.774 ± 130 ms, $p = 0.5$), ERP of RA (240 ± 14 vs. 246 ± 18 ms, $p = 0.6$), the mean maximal P wave duration (121 ± 8 vs. 125 ± 13 ms, $p = 0.3$), the mean PWD (28 ± 14 vs. 36 ± 12 ms, $p = 0.07$), mean maximal P wave amplitude (0.14 ± 0.05 vs. 0.13 ± 0.04 mV, $p = 0.5$), dimension of the left atrium (30 ± 7 vs. 33 ± 6 mm, $p = 0.4$), or end-diastolic

Table 1 Comparisons of the baseline characteristics, P wave morphology and cardiac echo parameters.

Variable	Positive AF vulnerability group (n = 12)	Negative AF vulnerability group (n = 38)	p
Sex (M:F)	5:7	19:19	0.5
Age (y)	45 ± 17	46 ± 13	0.7
Hypertension	1	6	0.7
BCL (ms)	746 ± 156	774 ± 130	0.5
Atrial ERP (ms)	240 ± 14	246 ± 18	0.6
Pmax (ms)	121 ± 8	125 ± 13	0.3
PWD (ms)	28 ± 14	36 ± 12	0.07
Vmax (mV)	0.14 ± 0.05	0.13 ± 0.04	0.5
LAd (mm)	30 ± 7	33 ± 6	0.4
LVEDD (mm)	45 ± 4	45 ± 5	0.9
LVSd (mm)	10 ± 2	9 ± 2	0.6
LVEF (%)	62 ± 9	70 ± 10	0.4

AVNRT = atrioventricular nodal reentry tachycardia; AVRT = atrioventricular reciprocating tachycardia; CL = cycle length; ERP = effective refractory period; IVSd = thickness of the interventricular septum; Lad = dimension of the left atrium; LVEDD = end diastolic dimension of the left ventricle; LVEF = Left ventricular ejection fraction; Pmax = maximal mean duration of P wave; PSVT = paroxysmal supraventricular tachycardia; PWD = mean P wave duration dispersion; Vmax = maximal mean amplitude of P wave.

dimension of the LV (45 $\pm$ 4 vs. 45 $\pm$ 5 mm, $p = 0.9$) and the LVEF (62 $\pm$ 9 vs. 70 $\pm$ 10%, $p = 0.4$) between the positive and negative AF vulnerability groups.

The mean duration of follow-up was 18 $\pm$ 9 months after catheter ablation. No patient had an ECG recording or symptoms suggesting significant tachyarrhythmia occurring during follow-up.

Discussion

In this study, AF or ATs could be induced in almost half (24/50 patients, 48%) of our patients with PSVT and without AF history after catheter ablation. However, only 24% of these induced ATs could be sustained longer than 10 seconds and the reproducibility of the results was low. Comparing RA ERP, sinus cycle length, maximal P wave duration, PWD, maximal amplitude of P wave, and echocardiographic parameters showed no significant difference between the positive and negative AF vulnerability groups. Of note, all patients had no evidence of significant tachyarrhythmia occurring during clinical follow-up.

Mechanisms of ATs have been proposed in previous studies [1,2]. Atrial substrate was believed to play an important role in the maintenance of ATs including AF. Many indices of atrial substrates, including ERP of the atrium, P wave duration, and PWD, have been suggested to be associated with property of atrial activation [13—16]. The heterogeneous changes of ERP in different areas of atrium were reported in patients with AF [17]. Longer P wave duration and the wider PWD were reported to be correlated with a longer and more heterogeneity of atrial activation and associated with more frequent occurrence of AF [16,18]. Furthermore, previous studies also demonstrated that older age, larger LA and impairment of LV function were associated with the occurrence of AF [19,20].

In this study, however, no indices of atrial substrates showed significant difference between patients with and without inducible ATs. The inducibility of the ATs or AF in our patients could not be predicted from the conventional atrial substrates indices used generally. As a result, further studies are needed to clarify the mechanisms involved in the inducibility of ATs in structural normal heart individuals.

All patients enrolled in this study had no evidence of other symptomatic ATs except PSVT. After elimination of the clinical documented PSVT, ATs were induced in 48% of patients by the atrial decremental pacing protocols. However, only 24% of these induced ATs could be sustained for longer than 10 seconds and the reproducibility of the results occurred in only 2/12 (17%) of the patients. This raises the question of what are the meanings and the significance of the ATs inducibility test (which is also frequently used as the AF vulnerability test) after AF catheter ablation.

Previous clinical studies have observed the relatively frequent occurrence of symptomatic AF in patients after successful catheter ablation of atrioventricular accessory pathways and found that older age and atrial vulnerability were the two independent predictors of AF occurrence [8,21]. Dagres et al. also demonstrated that old age, but not inducibility of AF, was a predictor of recurrence of AF in patients after catheter ablation of atrioventricular accessory pathway [8]. By using various different pacing protocols, Huang et al. also reported that about 27% of the PSVT patients without AF history could experience induced AF during cardiac electrophysiological study [22].

Pulmonary vein isolation and atrial substrate modification using catheter ablation have been developed to be one of the modalities to treat patients with drug-refractory, symptomatic AF. However, the reliable end-point of AF ablation is still not well defined. Previous studies demonstrated that noninducible ATs could predict the freedom from AF after catheter ablation [5,6]. A stepwise strategy for AF ablation using the inducibility as a guide for further ablation, has been proposed [6]. This stepwise strategy prevents the proarrhythmia induced by more advanced catheter ablation, which suggests that ATs need adequate atrial substrates for their maintenance. However, in the stepwise ablation strategy, further stepwise line ablation procedures may also ablate the autonomic nervous plexus and therefore modulate the autonomic function, which could be another mechanism to explain the improvement of the success rate of AF ablation other than substrate modification [23]. As a result, the clinical significance of the ATs inducibility test and its relationship to AF vulnerability both need more investigation to validate the claim.

There were many factors that might interfere with the result of inducibility of ATs during electrophysiological study, including: (1) site of the stimulation; (2) autonomic tone status of patients; (3) pacing protocol; and (4) the degree of the provocative tests.

The AF vulnerability test is usually performed after the AF pulmonary vein isolation and substrate modification to test the atrial substrate condition. Most of our patients in this study were AVNRT or AVRT; spot ablation was performed using 4 mm tip ablation catheter and limited atrial tissue was injured during the procedure. However, Chang et al. also showed that there was a different effect of atrial vulnerability and remodeling after the AF ablation between AF patients with AVNRT and AVRT [24]. The complexity of the relationship between the AF, PSVT, and decremental atrial burst pacing need to be further clarified.

In our study, the traditional indices of atrial substrates could not predict the inducibility of ATs. This result also suggested that the mechanisms of inducibility of ATs in those patients without history of AF might be different from those patients with clinically documented AF.

There are some limitations concerning this study that are worth noting. First, there was only one inducibility protocol used in our study; different protocols may result in different results. Second, the period of clinical follow-up was relatively short. Third, the patients enrolled in our study had no history of organic heart disease or AF. The results of this study cannot completely be applied to patients with AF or with organic heart disease.

In conclusion, ATs or AF could be induced in the patient with normal structural heart. The traditional clinical indices of atrial substrates were not significantly different between the positive and negative AF vulnerability groups in our patients. Protocols other than atrial burst decremental pacing should be investigated to evaluate the endpoint of the atrial substrate modification in catheter ablation of AF or other ATs.

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